O-GLCNAC TRANSFERASE INHIBITORS AND USES THEREOF

RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. § 119(e) to U.S. Provisional Application, U.S. Ser. No. 62/724,479, filed Aug. 29, 2018, which is incorporated herein by reference.

GOVERNMENT SUPPORT

[0002] This invention was made with government support under grant numbers GM094263 awarded by the National Institutes of Health (NIH). The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] The hexosamine biosynthetic pathway (HSP) is a minor branch of the glycolytic pathway, diverting 3-5% of cellular glucose toward the synthesis of UDP-GlcNAc, which is either transported to the Golgi and used in the synthesis of complex glycans or remains in the cytoplasm where it is the substrate for O-GlcNAc transferase (OGT). OGT is the sole known enzyme to catalyze the glycosylation of serine and threonine residues on many nuclear and cytoplasmic proteins (termed O-GlcNAcylation). This post-translational modification is dynamic and is a general mechanism, like protein phosphorylation, of signal transduction. O-GlcNAc transferase (OGT) is an essential mammalian enzyme that modifies myriad nuclear and cytoplasmic proteins with O-linked N-acetylglucosamine (O-GlcNAc), affecting their stability, localization, activity, and interactions with other proteins.[1] Evidence points to a crucial role for O-GlcNAc in metabolic homeostasis and elevated O-GlcNAc levels have been linked to metabolic adaptations associated with several disease phenotypes, including the abnormal proliferative capacity of cancer cells.[2] To better understand OGT function, small molecule OGT inhibitors are required. OGT inhibitors with some cellular activity have been reported, but most are substrate analogs that offer limited opportunities for modifications to improve potency or selectivity.[3]

[0004] Excess flux through the HSP has been implicated in both the early (insulin resistance) and late (nephropathy, microvascular damage) stages of diabetes mellitus, both in vivo and in vitro. Diabetes involves a deficiency in the availability and/or utilization of insulin. Insulin is a hormone produced by the pancreas and is necessary for cells to utilize glucose. Insulin resistance is a condition in which muscle, fat, and liver cells do not use insulin properly. As a result, the pancreas produces more insulin, which is also not used properly. Eventually, the pancreas cannot keep up with the body's need for insulin, and excess glucose builds up in the bloodstream. Thus, in insulin resistance, there may be high levels of blood glucose and high levels of insulin circulating in the bloodstream at the same time.

[0005] Experiments have shown that insulin resistance due to increased hexosamine flux is caused by hyper O-GlcNAcylation. Diabetics have increased production of two adipokines directly responsible for vascular injury, plasminogen activator inhibitor-1 (PAI-1) and transforming growth factor β1 (TGF-β1). Transcription of both of these proteins is decreased in cell culture when levels of O-GlcNAcylation are decreased. The molecular mechanism for this is known; increased transcription is mediated by the O-GlcNAcylation state of the transcription factor Spl.

[0006] OGT activity and O-GlcNAcylation have also been implicated in other disease states, such as neurodegenerative diseases, cancer, autoimmune diseases, and inflammatory diseases. Accordingly, there is a need to find OGT inhibitors useful as therapeutic agents.

SUMMARY OF THE INVENTION

[0007] Reversible glycosylation of nuclear and cytoplasmic proteins is an important regulatory mechanism across metazoans. One enzyme, O-linked N-acetylglucosamine transferase (OGT), is responsible for all nucleocytoplasmic glycosylation, and there is a need for potent, cell-permeable inhibitors to interrogate OGT function. The invention relates in part to compounds that inhibit O-GlcNAc transferase (OGT) activity. The inventive compounds are based on hits identified in a screen of over 1200 compounds for their ability to inhibit OGT. Described herein are OGT inhibitors based on a structure-based development of OGT inhibitors culminating in compounds with low nanomolar inhibitory potency and on-target cellular activity. In addition to disclosing useful OGT inhibitors, the structures disclosed herein provide insight into how to inhibit glycosyltransferases, a family of enzymes that has been notoriously refractory to inhibitor development. The active site of OGT is particularly challenging to inhibit. The nucleotide-sugar substrate, UDP-GlcNAc, lies in an extended conformation underneath the peptide substrate; filling the active site requires molecules that can mimic this stacked substrate geometry (FIG. **5**).[4] Complicating matters, OGT's active site is hydrophilic and accommodates many peptide sequences, with substrate selection being determined not by specific contacts to OGT side chains, but by binding of proteins to the tetratricopeptide repeat (TPR) domain.[5] At a loss for how to design inhibitors for OGT's large, hydrophilic, and promiscuous active site, a high-throughput screen that led to a weakly active compound containing a quinolinone-6-sulfonamide (Q6S) was previously carried out.[3b,6] Here structures of OGT complexed with several cell-permeable Q6S-based inhibitors are reported, including two having low nanomolar K_ds. These are the first known structures of a nucleotide-sugar glycosyltransferase complexed with biologically active inhibitors that are not substrate mimics. Compounds of the invention inhibit O-GlcNAcylation by OGT. O-GlcNAcylation is the glycosylation of serine and/or threonine residues on nuclear and cytoplasmic proteins that is catalyzed by OGT. Compounds of the invention are useful for the treatment of diseases and disorders associated with hyper-O-GlcNAcylation (e.g., diabetes and complications thereof, cancers, neurodegenerative diseases, autoimmune diseases, and inflammatory diseases).

[0008] In one aspect, the present disclosure provides compounds of Formula (I'):

(I')